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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,685	HAAHEIM, LARS REINHARDT	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,24-29 and 31-42* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,24-29 and 31-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-22,24-29 and 31-42* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed on April 4, 2006 is acknowledged and has been entered. Claims 23 and 43-46 have been cancelled. Claims 21, 22, 24, 31, 35, 37-39, 41, and 42 have been amended. The specification has been amended. Claims 1-20 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Claims 1-22, 24-29 and 31-42 are pending. Claims 21, 22, 24-29 and 31-42 are under examination.

Information Disclosure Statement

2. It is noted that only page 347 of the Yong Sung Choi reference is missing and excluded from the copy submitted. Accordingly, only the information referred to therein, which excludes that which is set forth in page 347, has been considered.

Withdrawn Rejections

3. All rejections not reiterated herein, have been withdrawn.

4. The rejections of claim 23 are now moot in light of Applicant's cancellation of the claim.

5. In light of Applicant's amendment, the rejection of claims 21, 22, 26, 33, 35, and 36 under 35 U.S.C. 102(b) as being anticipated by Choi (Biosynthesis and Secretion of

Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)), is hereby withdrawn.

6. In light of Applicant's amendment, the rejection of claims 21, 22, 25-29, 31, and 33-42 under 35 U.S.C. 102(b) as being anticipated by Atkinson et al. (Direct Measurement of Antibody Production in Cell Suspensions using ELISA, Journal of Immunological Methods 76: 365-373 (1985)), is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 21, 22, 24-29 and 31-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21, as amended, remains vague and indefinite because it is unclear how the claimed method can differentially determine between 1) the presence of, and 2) the amount of, newly synthesized target antibodies released from disrupted lymphocytes in the body fluid sample as required by the preamble, by merely detecting the target antibodies or parts thereof released from disrupted lymphocytes contained in the sample. At best, it appears that the recited method can only provide a qualitative determination of the presence of newly synthesized target antibody. Same analogous comment or problem applies to claim 22. See also claim 41.

Claim 21 also remains vague and indefinite because it is unclear how the target antibodies released from the disrupted lymphocytes are differentially detected and quantitatively determined from soluble antibodies or immunoglobulins released into plasma resulting from immunogen exposure prior to disruption of the lymphocytes. It appears, therefore, that the lymphocytes should be separated or isolated from the whole blood sample or the target antibodies released from disruption thereof should be differentially labeled from the soluble antibodies released from the lymphocytes prior to their disruption. Same analogous comment or problem applies to claim 22. See also claim 41.

Claim 34 is objected to for depending from a cancelled claim.

Claim 35 remains unclear and indefinite in having improper antecedent basis problem in reciting, "lymphocytes directly isolated from said blood sample are used in the method", because it defines that the instant lymphocytes in the claim are different or separate from those recited in claim 21 or 22. Hence, it is unclear what structural and functional cooperative relationship exists between the lymphocyte in the instant claim and those recited in claim 21 or 22. Does Applicant perhaps intend, "wherein the lymphocytes are directly isolated from said blood sample."

Claim 38 remains vague and indefinite because it is unclear what significant functional cooperative relationship exists between the "one or more antigens" recited in the instant claim and the other elements recited in the solid phase binding assay which requires that they "are contacted with the solid phase" for use in detecting the newly synthesized target antibodies. Are these antigens intended to provide a label.

Claim 39 remains vague and indefinite because it is unclear what significant functional cooperative relationship exists between the "one or more antibodies" recited in the instant claim and the other elements recited in the solid phase binding assay which requires that they "are contacted with the solid phase" for use in detecting the newly synthesized target antibodies. Are these antibodies intended to be conjugated to a label.

Claim 40 stands vague and indefinite because it is unclear how the "soluble substrate" is used for the detection step to yield a spectrophotometric signal. Is the target antibody labeled with an enzyme for reaction with soluble substrate to hence, produce a spectrophotometric signal. Please clarify.

Claim 40 provides for the use of "soluble substrate", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 21, 22, 24-29, 31, and 33-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choi (Biosynthesis and Secretion of Immunoglobulins,

Immunoglobulins, pages 345, 346, 348-351 (1981)) or Atkinson et al. (Journal of Immunological Methods 76: 365-373 (1985)) in view of Cox et al. (Kinetics of early immune response induced after parenteral influenza vaccination (Options for the control of influenza III, 561-571 (1996)).

Choi provides methods used to study production of newly synthesized antibodies (biosynthesis of immunoglobulins) in lymph node samples in response to immunogen exposure (see Introduction). Choi teaches obtaining a lymph node tissue sample and isolating (purifying) lymphocytes from the sample using Ficoll-Hypaque gradient centrifugation (see page 345 second and third full paragraph). Thereafter, the lymphocytes are cultured and stored (chilled) at about 4C or less (ice water bath (2-6C)) to separate the cells from incubation media containing secreted proteins. The lymphocytes are then disrupted (lysed) using nonionic detergent solution to solubilize cytoplasm without breaking the nuclei and to release newly synthesized proteins and antibodies. The released antibodies are detected using serological assay, which provides a measure of the amount of newly biosynthesized antibodies present in the lymphocytes present in the lymph node tissue sample (see page 346, first paragraph). Choi provides that secretion of newly synthesized antibodies (if secreted from lymphocytic cells) does not begin until 30 minutes after synthesis.

Atkinson et al. provide an enzyme-linked immunosorbent assay (ELISA) method for direct measurement of newly synthesized antibody being produced in immune cells, i.e. synthetic capacity, in response to immunogen exposure (anamnestic response to immunization). Atkinson et al. teach obtaining an immune spleen or lymph node sample

containing lymphocytes from mice, isolating [nucleated] lymphocytic cells by Ficoll-Hypaque gradient centrifugation, eliminating [secreted] antibody carry-over by multiple washing of the lymphocytes, and disrupting the cells using physical disruption (freeze-thaw method and sonication) to release newly synthesized antibodies from the cells. After preparation of the sample for assay, Atkinson et al. adds a sample volume of less than 1 ml. (200 ul) into multiple solid phases having one or more antigens immobilized thereto (antigen-coated wells) in a microtiter plate. One or more antibodies (biotinylated anti-mouse immunoglobulin) are also added and coated into the solid phase (see page 367 in its entirety). Atkinson et al. use highly sensitive avidin-biotinylated peroxidase (ABC) reagents and soluble substrate (orthophenylenediamine) to detect and measure the amount of newly synthesized antibodies by ELISA (see page 365, page 366, and 368 in their entirety). According to Atkinson, the lymphocytes should be stored and equilibrated at 4C after initial suspension in order to decrease the rate of antibody synthesis and secretion prior to the method (see page 369 in its entirety). Antibody production by different cell populations can be compared relative to standard controls included in each microtiter plate. Atkinson et al. teach using negative control antigen (irrelevant antigen or bovine serum albumin) as standard (see page 367).

Choi or Atkinson et al. have been discussed supra. Choi or Atkinson et al. differ from the instant invention in failing to teach detecting newly synthesized antibody in peripheral blood samples.

Cox et al. studies kinetics of early immune response induced after immunogen exposure (parenteral influenza vaccination). Cox et al. use different samples including

peripheral blood, serum, and oral fluid. In study, in vitro cultures of peripheral blood lymphocytes were obtained and tested for antibody response to the immunogen exposure by detecting or determining for the presence of IgG, IgM, and IgA in the sample. See Abstract, page 565 (The antibody secreting cell response in peripheral blood), and page 567 (The antibody secreting cell response in tonsils).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the method as taught by Choi or Atkinson on peripheral blood samples as taught by Cox because Cox provided that lymphocytes used in the method of Choi and Atkinson, can be obtained and cultured from peripheral blood samples for use in testing antibody production in response to parenteral influenza vaccination; hence, peripheral blood appears to constitute an obvious variation of sample routinely used in the art, upon which lymphocytic cells can be obtained for use in antibody production assays.

9. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)) or Atkinson et al. (Journal of Immunological Methods 76: 365-373 (1985)) in view of Sison A V (Laboratory Methods for early detection of HIV-type-1 in Newborns and Infants, (Clinical Microbiology Reviews, 5(3): pp. 238-247 (July 1992)).

Choi and Atkinson et al. have been discussed supra. Choi and Atkinson et al. differ from the instant invention in failing to teach detecting newly synthesized

antibodies in neonate or infant blood samples to distinguish between newly synthesized antibodies from the infant and passively transferred maternal antibodies.

Sison teaches determining in vitro antibody production and using ELISA Spot assay to test for immunogenic exposure of infant or neonate to the HIV-1 virus. In practice, Sison teaches obtaining peripheral blood lymphocytes from infants, isolating and culturing the lymphocytic cells in vitro, subjecting the cells to immunogen activation, i.e. pokeweed, and detecting for the production or presence of anti-HIV-1 antibody using HIV-1 antigen coated solid phase (polystyrene wells). Sison uses this test to distinguish between newly synthesized antibodies from the infant and transferred maternal antibodies during pregnancy. See Abstract and page 241, column 1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect newly synthesized antibodies using the method taught by Choi or Atkinson on neonatal or infant blood samples as taught by Sison because Choi and Atkinson specifically taught that their methods specifically detect biosynthesis of antibodies in specific cells, such as those that are derived from neonatal cells as in the teaching of Sison, where he specifically emphasized the need to separate and distinguish between neonatal derived antibodies and maternally transferred antibodies. One of ordinary skill in the art at the time of the instant invention would have been motivated to detect for the presence of newly synthesized antibody using the method of Choi or Atkinson, in samples obtained from infants or neonates as taught by Sison, because Sison specifically taught that antibody production, i.e. of newly synthesized

antibodies, in neonatal [lymphocytic] cells provides specific diagnostic information on immunogen exposure and infection for infants.

Response to Arguments

10. Applicant's arguments with respect to claims 21, 22, 24-29, and 31-42 have been considered but are moot in view of the new grounds of rejection.

A) Applicant incorporated the limitation recited in claim 24 into independent claim 21 (wherein the sample is a blood sample or a lymphocyte preparation therefrom), and submits that the pending claims encompass detection of newly synthesized antibodies, and that prior to the invention, it was not known, disclosed, nor suggested that such antibodies existed in lymphocytes in any significant amount prior to secretion, and that lysis of lymphocytes could yield enough antibody for detection and use as a marker or diagnostic tool. Applicant then argues that all known assays, including those currently of record (Atkinson), detect secreted antibodies using long incubation times in vitro to allow accumulation of sufficient antibodies for detection.

In response, Applicant's argument is not persuasive because the claims, even as currently amended, do not exclude the long incubation times taught by the combined teaching of Choi or Atkinson and Cox. Specifically, the long incubation times taught by the combined teaching of Choi or Atkinson and Cox read on the claimed invention because the "incubating periods" appear to be a form of a disruption to the lymphocytes which causes for any newly synthesized antibody to be released or secreted from within the confines of the lymphocytic cell membrane such that they may be detected. The

specification at page 8, first full paragraph, only exemplifies cell lysis or freeze-thaw incubation cycles, as forms of lymphocyte disruption.

Further responsive to Applicant's argument, the cell-based ELISA modification as taught by Choi and Atkinson provides a measure of newly synthesized antibodies as claimed because the step of detecting target antibodies released from lysed lymphocytes contained in a sample is consonant to that provided by Choi and Atkinson.

B) Applicant argues that Choi and also Sison do not teach or suggest the claimed invention because Choi and Sison only detect antibodies that are synthesized in vitro, hence, the references do not involve newly synthesized antibodies. Applicant then contends that Choi or Sison in combination with other references cannot render obvious the claimed invention.

In response, the claims, albeit drawn to newly synthesized antibodies, as recited and in light of the specification, do not appear to exclude in vitro synthesis as part of the newly synthesized antibodies. Accordingly, Choi and Sison in combination with Atkinson and Cox, are deemed to suggest the claimed invention.

11. No claims allowed.

12. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
June 12, 2006

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08/11/06